Visceral analgesics and functional dyspepsia: have we found the Holy Grail?

One of the commonest problems presenting in gastrointestinal practice is the patient with chronic or recurrent epigastric pain or discomfort where routine diagnostic testing has failed to identify a definite structural cause for the symptoms. Empiric antisecretory and prokinetic agents remain the mainstay of treatment for patients with a diagnosis of functional (or non-ulcer) dyspepsia, but only a minority experience complete symptom relief with these agents. Rational medical treatment for patients with functional dyspepsia remains an elusive goal partly because functional dyspepsia seems to comprise a heterogeneous syndrome. For example, approximately 50% of patients have Helicobacter pylori gastritis, up to 50% have delayed gastric emptying and perhaps 50% of patients have visceral hypersensitivity to mechanical distension of the stomach or duodenum; clearly, these pathophysiological subsets overlap, although visceral hypersensitivity is currently postulated to be of central importance. In addition to being sensitive to mechanical distension, patients with functional dyspepsia as a group may be more sensitive to other stimuli such as pentagastrin injection or intragastric infusions of acid, saline and pancreatic or biliary secretions. Although there is heightened visceralnociception, somatic pain sensation is normal suggesting that the sensory defect is localised to the gastrointestinal tract, although these observations may also be explained by aberrant processing of signals at the spinal cord or central nervous system level. Patients with the irritable bowel syndrome (IBS) have well documented visceral hypersensitivity to mechanical distension of the colon and small bowel. Furthermore, rectal hypersensitivity seems to be inducible in patients with IBS following mechanical stimulation of the sigmoid colon. About one third of patients with functional dyspepsia have concurrent symptoms of IBS. Indeed, it has been postulated that IBS and functional dyspepsia represent the two ends of the same disease spectrum in at least a subset of patients.

Vagal and spinal (splanchnic) afferent mechanoreceptors, with receptive fields primarily located in the gastric wall, are believed to mediate conscious perception of excessive gastric distension. There has therefore been great interest in developing drugs that selectively target sensory receptors mediating visceral sensation. Opioid agonists such as morphine produce analgesia by blocking the activation of sensory nerve cells; the actions of the opioid agonists in vivo depend on the receptors that they bind to and act upon, and their distribution. The major opioid receptors (\(\delta\) and \(\kappa\)) are located in the enteric nervous system probably on the distal ends of primary afferent neurons and in the submucosal and myenteric plexus; a multitude of opioid receptor subtypes seems to exist. Fedotozine, a synthetic ligand, is a modestly selective peripheral kappa (\(\kappa\)) subtype 1a opioid agonist. In healthy volunteers, fedotozine has been shown to increase significantly the pressure necessary to induce discomfort from mechanical distension of the stomach, without altering gastric compliance or peripheral pain thresholds. Other classes of drugs that may also act as selective visceral analgesics include the serotonin (both 5HT\(_3\) and 5HT\(_4\)) antagonists and the somatostatin analogue octreotide as well as mast cell inhibitors and neurokinin antagonists, to name a few.

Clinical trials of visceral analgesics are of increasing interest but what should be defined as an acceptable treatment goal in functional dyspepsia? A recent systematic review of treatment trials in functional dyspepsia concluded that most of the trials in this field had major methodological limitations, particularly in relation to assessment of symptoms. From the patients' perspective, a substantial improvement or abolition of symptoms with a resultant improvement in quality of life must be the outcome of choice. Indeed, the proportion of patients who obtain total symptom relief, rather than change in an arbitrary symptom score, is likely to represent the most believable endpoint for clinicians in practice; statistical outcomes such as applying Cohen's effect size index (dividing the difference between group means by the common standard deviation) or other artificial statistical manipulations are unlikely to be perceived as being very meaningful.

In this context, the clinical trial results reported by Read et al in this issue (see page 664) are of major interest. A large cohort of patients (n=333) was randomised after a placebo run-in to six weeks of fedotozine (30 mg three times daily) or placebo. A significant improvement in the intensity of the overall symptom score as well as epigastric pain and nausea was observed, but inability to finish a normal meal and "slow digestion" did not improve significantly. Importantly, clinical significance needs to be dissected out from the statistical results. For example, in patients on fedotozine, the dyspepsia intensity score decreased from a mean of 1.6 at baseline (where the maximum possible score was 5 and the minimum score 0) to 1.1 at six weeks, while with placebo the mean scores also decreased from 1.5 to 1.2! The size of the treatment effect raises the issue of statistical versus clinical significance; a large enough study may detect statistically significant differences of a drug over placebo that do not translate into a real clinical benefit, and this seems to apply in Reed et al's study. Notably, similar results were reported in functional dyspepsia by Fraitag et al.

Other trials have reported a small but significant benefit of fedotozine in IBS. It is notable that while the patients in Read et al's study were all diagnosed as having functional dyspepsia, the majority (73%) had concurrent IBS and this is greater than might be expected by chance. Indeed, the overall abdominal pain score improvement observed in Read et al's trial is very similar to the results reported in IBS. However, it is unclear whether or not the co-occurrence of IBS impacted on the observed results; more substantial effects might have been found if patients with functional dyspepsia only had been enrolled.
Data from animal studies suggest that the antinociceptive effect of the opioids may be mediated mainly through suppression of inflammation by inhibiting excitatory neurotransmitter release (eg substance P) from sensory nerves.\textsuperscript{8, 9, 10} Therefore, the subset of patients with functional dyspepsia who have histological gastritis or duodenitis may be the most likely to respond to fedotozine. Duodenitis was not assessed by Read and colleagues, but in the group of patients where antral biopsy samples were available (49%), \textit{H pylori} gastritis was not shown to influence the treatment outcome. This may indicate that the very modest visceral analgesic effects of fedotozine in humans are independent of gut inflammation, but in future studies this issue needs to be tackled more carefully.

The symptom improvement observed with fedotozine is comparable to the efficacy of the prokinetic agents domperidone and cisapride, although these have been more convincingly documented to be superior to placebo in reducing the symptoms of functional dyspepsia.\textsuperscript{2} However, only domperidone potentially has a gastric motility.\textsuperscript{1} Indeed, the mode of action of domperidone and cisapride, although these have been comparable to the efficacy of peripheral kappa agonist, is unexplained.

There are many receptors mediating visceral sensation. It is therefore not surprising that blockade of one receptor subtype does not lead in most patients to abolition of symptoms. Notably, there is actually a relative paucity of \textit{k} receptors compared with other opioid receptors in the enteric nervous system, at least in animal studies.\textsuperscript{10} Moreover, many other factors may influence nociceptive pathways including immune cells and neurotrophic factors\textsuperscript{8} which may explain the marginal clinical efficacy of fedotozine. While the goal of targeting visceral perception in the functional gastrointestinal disorders is laudable, the current approaches will presumably remain hit and miss until the interaction of the various sensory receptors in the gastrointestinal tract and their links with spinal and higher centres has been explored and understood. We need drugs that truly will normalise the relevant disturbed physiology in functional dyspepsia (which is not yet well enough defined). This goal must remain the Holy Grail if cure as opposed to temporisation of symptoms is to be achieved.

NICHOLAS J TALLEY

Professor of Medicine,
University of Sydney,
Clinical Sciences Building,
PO Box 63, Penrith, NSW 2751,
Australia